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9. Summary

Role of ATP- sensitive potassium channels in the regulation of oxidative metabolism and circulative activity in cattle

Background - High intake of metabolizable energy poses risk to metabolic disorders. KATP channels are therapeutic targets but their pharmacological sensitivity changes with altered subunit composition. In addition, sensitivity changes in cardiovascular diseases associated with metabolic disorders occurring in high intake of metabolizable energy. This suggests the possibility that subunit composition is a dietary target. The aim of the study was to examine this hypothesis.

Methods and Results – Young bulls (300±10 days old and 295±15 kg in weight) were fed 1.5- and 2.0-fold metabolizable energy for maintenance (MEm), four in each group. This feeding schedule corresponded to moderately restricted and ad libitum metabolizable energy intake and induced significant ($P<0.05$) different metabolic rates at rest (601 and 656 $kJ/kg^{0.75}d$) measured by indirect calorimetry. Higher resting metabolic rate corresponded to an elevated heart rate at rest (60±5 versus 71±8 beats/min in the 1.5- and 2.0-MEm groups, $P<0.05$).

The animals were treated with levcromakalim (80 nmol/kg), an opener of KATP channels (KCO), using a dose of 80 nmol/kg and levcromakalim post-glibenclamide (480 nmol/kg), an inhibitor of KATP channels (KCJ). Oppositely to the 1.5-MEm group, meal-evoked heart rate was reduced in the 60 min period but substantially increased in the 400-500 min period post-KCO, responses abolished by KCJ pre-treatment, indicative for specific results mediated by KATP channels.

KCO inhibited a meal-induced saphenous vein flow in the 2.0-MEm group measuring the flow by an electromagnetic probe. In contrast the 1.5-MEm group responded to a treatment with KCO with a meal-induced flow higher than the control (administration of the solvent). The density and the affinity to glibenclamide of sulfonylurea receptors was analyzed using a fluorescent derivative of glibenclamide, glibenclamide Bodipy, in ventricular and saphenous vein myocytes and cytoflowmetric detection of the fluorescence intensity/single cell. The equilibrium dissociation constant of ventricular myocytes from the 1.5-MEm group differed significantly from the constant of ventricular myocytes from the 2.0-MEm

group in contrast to saphenous vein myocytes, suggesting diet induced changes in glibenclamide binding properties occurred at the cardiac level.

An analysis of ventricular transcripts by reverse transcription – DNA polymerase chain reaction (RT-PCR) was performed by specific primers for mRNA encoding SUR2, Kir6.1 and Kir6.2 proteins. Electrophoretic separation revealed a shift from SUR2A to SUR2B transcripts comparing the RT-PCR products of the 1.5-MEm with the 2.0-MEm groups. Thus, predominant expression of SUR2B was accompanied with elevated heart rate and metabolic rate.

Conclusions – KATP channel constituents are diet-responsive, thereby high intake of metabolizable energy can alter channel composition. This change may have physiological consequences indicated by glibenclamide binding in vitro and by the responses of the heart rate and venous flow to the KATP opener, levcromakalim, since they were reduced or abolished by glibenclamide. As heart rate and metabolic rate are correlated, the results strongly suggest involvement of KATP channels in the metabolic regulation of whole animals and changes in KATP channel composition contribute to changes in their function.